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14. ABSTRACT

Tuberous Sclerosis Complex (TSC) is a genetic disorder resulting from mutations in either the TSC1 or TSC2 genes. TSC is characterized by abnormal skin pigmentation and tumor formation in multiple organ systems. The TSC1 and TSC2 gene products are involved in cell signaling; in particular they are involved in the mammalian target of rapamycin (mTOR) signaling pathway. In TSC, the epidermal basal cells contain a mutant copy of either the TSC1 or TSC2 gene. A loss of heterozygosity results in constitutive activation of mTOR leading to production of epidermal cells at a faster rate than the ability to slough the dead cells. This overproduction of skin cells, in conjunction with angiogenesis, reslults in the formation of visible facial angiofibromas over time. The lesions appear as red or pink papules distributed over the central face, especially on the nasolabial folds, cheeks, and chin. Lesions appear in early childhood and are present in up to 80% of TSC patients. Facial angiofibromas create considerable cosmetic morbidity for patients with TSC and currently there is no effective method for preventing or permanently removing them. Rapamycin is a naturally occurring antifungal macrolide that binds with high specificity to mTOR resulting in inhibition of mTOR activity and ultimately in downregulation of cell growth. Systematically administered rapamycin has an unfavorable side effect profile, limiting its potential use. Commonly reported side effects include oral ulcers, hyperlipidemia, thrombocytopenia, acneiform rash, immunosuppression, and impaired wound healing. Rapamycin has a molecular weight of 914.2 grams, allowing for its absorption through the superficial layers of the epidermis. With an appropriate delivery system, topically applied rapamycin should be able to penetrate the skin and reach the deep epidermal basal cells implicated in development of facial angiofibromas without causing side effects seen with systemic administration. This project is a multi-center prospective, randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of a topically applied formulation of rapamycin to cutaneous angiofibromas in subjects with TSC. The primary goal is to evaluate the efficacy of the topical medication to reduce the appearance of cutaneous angiofibromas in patients with TSC. The secondary goal of this study is to confirm the safety of the topical medication. During the 1st year of the project, pre-clinical evaluations have occurred to ensure the purity, bioavailability, stability, and lack of cumulative irritation of the investigational product. The research protocol has been reviewed by independent review boards at each sites where study subjects are being enrolled and individual study sites are being trained on trial procedures and protocols. During the 1st, 2nd, and 3rd years of the project, 230 subjects will be enrolled into the study. Following enrollment, study subjects will apply either a skin coating containing rapamycin or a skin coating alone nightly to their angiofibromas. Each subject will use the investigational product for a total of 6 months. Photodocumentation will occur monthly and rapamycin blood levels will be drawn to confirm lack of absorption. Following completion of the study, photographs will be evaluated by an independent dermatologist blinded to both the treatment arm and the stage of treatment. The dermatologist will assess each photograph's appearance using the angiofibroma grading scale and will compare photographs taken at study visit 1 (prior to treatment) and study visit 7 (upon completion of treatment).

15. SUBJECT TERMS
None provided.

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Technical Report
Topical Rapamycin Therapy to Alleviate Cutaneous Manifestations of TSC
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INTRODUCTION

Tuberous Sclerosis Complex (TSC) is a genetic disorder characterized by abnormal skin pigmentation and tumor formation in multiple organ systems. TSC affects 1 in 7000 individuals worldwide. Common symptoms of TSC include: learning disabilities, mental retardation, seizures, skin lesions, kidney tumors, lung disease, heart tumors, and brain tumors. Facial angiofibromas are benign skin tumors found on the faces of patients with TSC. The angiofibromatous lesions appear as red or pink papules distributed over the central face, most notably on the nasolabial folds, cheeks, and chin. Lesions appear in early childhood and are present in up to 80% of TSC patients. These facial lesions create considerable cosmetic morbidity for patients with TSC. Since the initial descriptions of facial angiofibromas in the 19th Century, multiple treatments have been developed attempting to alleviate the appearance of these lesions. Treatments have included curettage, cryosurgery, chemical peels, dermabrasian, shave excisions, and laser therapy. Although the majority of these treatments are initially effective, they are uncomfortable and over time the lesions recur. Currently there is no effective method for preventing or permanently removing facial angiofibromas in patients with TSC. This study is designed to see if an investigational product nightly to their lesions for six months. The goal of this study is to develop a form of rapamycin that will provide a safe, effective treatment for facial angiofibromas in patients with tuberous sclerosis complex.

REPORT

Specific Aim 1: Obtain appropriate regulatory approvals and complete the preclinical evaluation of the topical product.

- Under the PI's supervision, Doyle's Pharmacy is responsible for the formulation, chemistry, manufacturing and control of the drug product.
    1. The study drug and controls have been successfully formulated and optimized with rapamycin concentrations of placebo (0.00%), low dose (0.10%), high dose (1.0%).
    2. Testing has shown stability for at least 180 days of the drug formulation. Doyle's Pharmacy continues to monitor drug stability to determine the maximum length of stability of the newly formulated drug product.
    3. Doyle's Pharmacy is manufacturing the study drug adhering to FDA Good Manufacturing Practices for distribution to study subjects via individual study sites.

Specific Aims 2 and 3: Determine if the application of the topical rapamycin to the skin reduces the appearance of facial angiofibromas in TSC. Confirm the lack of systemic uptake of topically applied rapamycin and monitor for adverse events.

- The research protocol has been approved by the University of Texas at Houston (primary site) Internal Review Board (IRB) and the Department of Defense Human Research Protection Office (HRPO).
- The protocol has been approved by the following collaborating site's local IRBs and HRPO: Minnesota, University of Alabama at Birmingham, Sydney, Australia, Texas Scottish Rite Hospital, Oakland Children's Hospital, Cincinnati Children's Hospital, University of California at Los Angeles, Massachusetts General Hospital, and Kennedy Krieger Institute.

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- Site initiation visits have been done for all sites except Kennedy Krieger Institute which is scheduled for October 10, 2013.
- All sites except Kennedy Krieger Institute are enrolling subjects.
- Trial monitoring is done throughout the study and site visits will be performed as selected sites arrive at the midpoint of the study for their sites. Trial monitoring has been performed at Oakland Children's Hospital and is scheduled for Texas Scottish Rite Hospital on October 18, 2013 and Massachusetts General Hospital on October 25, 2013.
- Safety monitoring is done monthly with review of lab results and case report forms by Patti Tate and Dr. Joshua Samuels.
- Adverse Events and Serious Adverse Events are reviewed by Patti Tate, Dr. Joshua Samuels and Dr. Gretchen Von Allmen. The DSMB will meet when 50 subjects have completed the study. The meeting is anticipated for the end of October.
- Data analysis will be done when all sites have completed enrollment and all study visits.
- Dissemination/Sharing of Results will be completed with publication of a manuscript when all the sites have completed the study and data has been analyzed.

KEY RESEARCH ACCOMPLISHMENTS

- The study drug has been successfully formulated and stability proven. It has been successfully manufactured in large batches for site distribution.
- Research protocols have been approved through local IRB and HRPO for all 10 clinical sites.
- Photography training has been completed and site initiation visits performed for all sites except Kennedy Krieger Institute and the training is scheduled for October 9, 2013.
- All sites except Kennedy Krieger Institute have begun enrolling and they are expected to start as soon as their photography training and site initiation visit are completed.

REPORTABLE OUTCOMES

- As of the date of this report, there have been 78 subjected completed. There has not been any data analyzed at this point so there are not any outcomes to report.
- The DSMB is anticipated to meet the end of October. Following initial safety review, any reportable outcomes will be assessed.
- The independent dermatologists have been chosen and the procedures for the photographic review are being finalized.

➢ Site→	HOU	MSP	BIR	DAL	BOS	CIN	BAL	LOS	OAK	SYD	Total	Comments
Enrolled	31	10	17	16	9	10	N/A	N/A	9	20	122	BAL and LOS not enrolling at time of report
Withdrawal	2	3	0	2	3	2	-	-	1	2	15	
Deviations	8	0	0	2	2	13	-	-	0	0	25	
AE/SAE	5/2	2/0	8/1	2/0	1/2	7/0	-	-	1/0	7/0	33/5	
Male/Female	14/17	4/6	9/8	7/9	-	4/6	-	-	6/3	6/14		Boston has not reported M/F
Caucasian/White	25	10	8	13	8	8	-	-	N/A	20	92	Race/ethnicity is not collected at OAK

Black/African American	0	0	3	0	0	2/2 AA/C	-	-	N/A	0	5	Biracial AA/C @ CIN
Hispanic/Latino	6	0	2	3	1	0	-	-	N/A	0	12	
Asian	0	0		0	1	0	-	-	N/A	0	1	
Native Hawaiian/Pacific Islander	0	0	1	0	0	0	-	-	N/A	0	1	
Age 1-6	6	0	0	0	1	0	-	-	0	4	11	Dallas sees only children
Age 7-12	1	1	2	9	2	0	-	-	3	5	23	
Age 13-18	7	4	5	7	4	4	-	-	1	4	35	
Age 19-25	10	1	3	0	0	4	-	-	3	2	23	
Age 26-30	4	1	0	0	2	0	-	-	0	0	7	
Age 31-35	0	1	4	0	0	1	-	-	1	1	8	
Age 36-40	1	0	0	0	0	0	-	-	1	2	4	
Age 41-45	1	0	3	0	0	1	-	-	0	1	6	
Age 46-50	1	0	0	0	0	0	-	-	0	1	2	
Age over 50	0	2	0	0	0	0	-	-	0	0	2	
Complaints	0	0	0	0	0	0	N/A	N/A	0	0	0	

CONCLUSION

- All sites have begun enrollment. Study subjects and investigators have noticed a subjective improvement in some study subjects, but as the data has yet to be analyzed, no conclusive evidence of efficacy has been drawn.
- The only protocol change is the reduction of labs for the rapamycin levels to visits 2 and 7 unless clinically indicated. The rapamycin levels obtained range from 0.0-1.2 with the non-detectable range <2 as determined by the standard laboratory values.
- Completion of the study, including the publication of the results, is expected by the summer of 2014.

REFERENCES

- The only new publication in this area is a case series in the Journal of Child Neurology by James W. Wheless and Hassan Almoazen published online May 16, 2013. http://jcn.sagepub.com/content/28/7/933

APPENDICES

- None.

SUPPORTING DATA

- None.